BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

OK

(3)

(12) UK Patent Application (19) GB (11) 2 265 900 (13) A

(43) Date of A publication 13.10.1993

(21) Application No 9307342.7

(22) Date of filing 07.04.1993

(30) Priority data
(31) 9207591 (32) 07.04.1992 (33) GB

(71) Applicant
Glaxo Group Limited

(Incorporated in the United Kingdom)

Glaxo House, Berkeley Avenue, Greenford, Middlesex, UB6 0NN, United Kingdom

(72) Inventor
Stephen Paul Watson

(74) Agent and/or Address for Service
C L Brewer
Glaxo Holdings plc, Glaxo House, Berkeley Avenue, Greenford, Middlesex, UB6 0NN, United Kingdom

(51) INT CL[5]
C07D 307/58 231/12

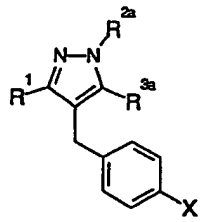
(52) UK CL (Edition L)
C2C CAA CAB CMB CMD CTZ CWK C1173 C1400 C1464 C1471 C215 C22Y C220 C225 C226 C246 C25Y C250 C252 C253 C28X C30Y C305 C31Y C315 C326 C351 C352 C36Y C360 C361 C386 C50Y C502 C62Y C623 C625 C652 C666 C669 C699 C760 C777 C802
U1S S1347

(56) Documents cited
EP 0446062 A1

(58) Field of search
UK CL (Edition L) C2C CMD CTZ
INT CL[5] C07D
Online databases: CAS ONLINE

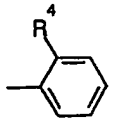
(54) Furanone intermediates in pharmaceutical pyrazole preparation

(57) Pharmaceutically active pyrazoles of formula (Ia)



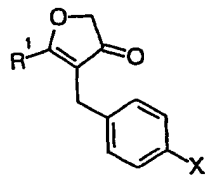
(Ia)

wherein
R^1 represents a hydrogen atom or a group selected from C_{1-6}alkyl or C_{2-6}alkenyl;
R^{2a} represents a hydrogen atom or a group selected from C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, C_{3-6}alkenyl, fluoroC_{1-6}alkyl or fluoroC_{3-6}alkenyl;
R^{3a} represents a hydroxymethyl group;
X represents a hydrogen atom or a halogen atom or a group of the formula



; and

R^4 represents a group selected from $-NH_2$, -CN, or a protected derivative of $-CO_2H$, a protected derivative of $-NH_2$ or an optionally protected C-linked tetrazolyl group;
are prepared by reacting a novel furanone of formula (IV)



(IV)

with a hydrazine of f rmula (III)

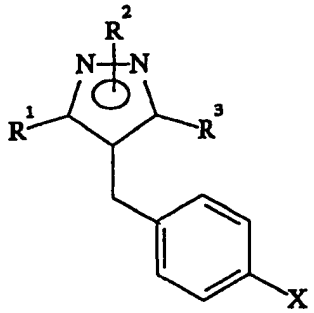
$R^{2a}HNNH_2$ (III)

GB 2 265 900 A

FURANONE INTERMEDIATES AND THE USE THEREOF

This invention relates to novel compounds which are useful as intermediates in the preparation of pharmaceutical compounds, to processes for their preparation, and to their use in the preparation of pharmaceutical compounds.

European Patent Specification No. 0446062A describes intermediate compounds of formula (I)



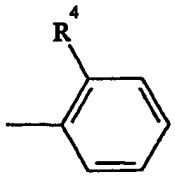
(I)

wherein R^1 represents a hydrogen atom or a group selected from C_{1-6}alkyl or C_{2-6}alkenyl;

R^2 represents a hydrogen atom or a group selected from C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, C_{3-6}alkenyl, fluoroC_{1-6}alkyl, fluoro C_{3-6}alkenyl, phenyl, $-(CH_2)_kCOR^5$ or $-(CH_2)_kSO_2R^5$;

R^3 represents a hydrogen atom or a group selected from C_{1-6}alkyl optionally substituted by a hydroxy or C_{1-6}alkoxy group, C_{2-6}alkenyl, fluoroC_{1-6}alkyl, $-(CH_2)_mR^6$, $-(CH_2)_nCOR^7$ or $-(CH_2)_pNR^8COR^9$;

X represents a halogen atom or a group of the formula



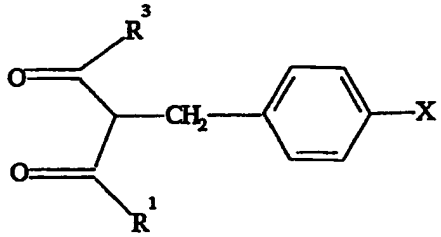
;

R^4 represents a group selected from $-NH_2$, -CN or a protected derivative of $-CO_2H$, a protected derivative of $-NH_2$ or a protected derivative of a C-linked tetrazolyl group;

R^5 represents a group selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy or the group $-NR^{10}R^{11}$;
R^6 represents a phenoxy or benzyloxy group;
R^7 represents a hydrogen atom or a group selected from hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, phenyl, phenoxy or the group $-NR^{10}R^{11}$;
R^8 represents a hydrogen atom or a C_{1-6}alkyl group;
R^9 represents a hydrogen atom or a group selected from C_{1-6}alkyl, C_{1-6}alkoxy, phenyl, benzyl, phenoxy or the group $-NR^{10}R^{11}$;
R^{10} and R^{11}, which may be the same or different, each independently represent a hydrogen atom or a C_{1-4}alkyl group or $-NR^{10}R^{11}$ forms a saturated heterocyclic ring which has 5 or 6 members and may optionally contain in the ring one oxygen atom;
k represents zero or an integer from 1 to 4;
m represents an integer from 1 to 4;
n represents zero or an integer from 1 to 4; and
p represents an integer from 1 to 4.

In particular, the compounds of formula (I) wherein the group R^2 is on the nitrogen atom adjacent to the group R^3 are to be preferred.

European Patent Specification No. 0446062A describes several methods for the preparation of the compounds of formula (I) as defined above. Thus, for example, a compound of formula (II)



(II)

may be reacted with a hydrazine of formula (III)

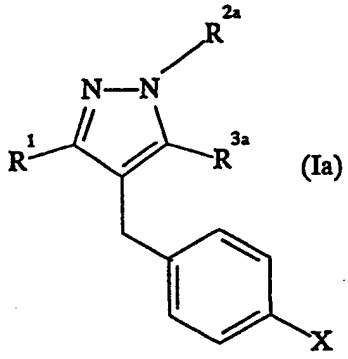
$$R^2NHNH_2 \quad \text{(III)}.$$

Alternatively, a compound of formula (I) may be prepared by interconversion of a compound of formula (I) wherein R^2 represents a hydrogen atom into a compound of formula (I) wherein R^2 represents a

C_{1-6}alkyl, C_{3-7}cycloalkyl or C_{3-7}cycloalkylC_{1-4}alkyl group, or a group of formula $-(CH_2)_kCOR^5$ or $-(CH_2)_kSO_2R^5$ where k is 1 to 4, by an alkylation reaction with a corresponding alkylating agent, for example, an alkyl halide such as an alkyl iodide.

The product of such reactions is a mixture of regioisomers (as is evident from the worked examples in EP-A-0446062). There is therefore a need for a more regioselective synthesis of the compounds of formula (I) in order to prepare the preferred compounds wherein the group R^2 is on the nitrogen atom adjacent to the group R^3.

Thus, the present invention provides a process for the preparation of a compound of formula (Ia)



(Ia)

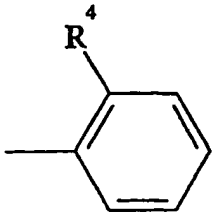
wherein

R^1 represents a hydrogen atom or a group selected from C_{1-6}alkyl or C_{2-6}alkenyl;

R^{2a} represents a hydrogen atom or a group selected from C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, C_{3-6}alkenyl, fluoroC_{1-6}alkyl or fluoroC_{3-6}alkenyl;

R^{3a} represents a hydroxymethyl group;

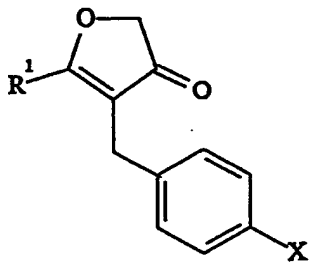
X represents a hydrogen atom or a halogen atom or a group of the formula



; and

R^4 represents a group selected from $-NH_2$, -CN, or a protected derivative of $-CO_2H$, a protected derivative of $-NH_2$ or an optionally protected C-linked tetrazolyl group;

which comprises reacting a compound of formula (IV)



(IV)

(wherein R^1 and X are as previously defined) with a hydrazine of formula (IIIa)

$$R^{2a}HNNH_2 \qquad \text{(IIIa)}$$

(wherein R^{2a} is as defined above).

The reaction is optionally effected in a solvent such as acetonitrile, an aqueous alcohol e.g. ethanol, an ether e.g. tetrahydrofuran or a substituted amide e.g. dimethylformamide, at a temperature in the range of 0°C to the reflux temperature of the solvent.

A preferred embodiment of the invention comprises the reaction of a compound of formula (IV) wherein R^1 represents a C_{1-5}alkyl, especially an ethyl, n-propyl or n-butyl, group and X is as defined above, with a hydrazine of formula (IIIa) wherein R^2 represents a C_{1-5}alkyl, especially an ethyl, isopropyl or n-butyl, group. Also preferred are those compounds wherein R^2 represents a C_{3-5}cycloalkylC_{1-2}alkyl, especially cyclopropylmethyl, group.

It will be appreciated that the product of the reaction between a compound of formula (IV) and a hydrazine of formula (IIIa) corresponds to a compound of formula (I) wherein R^3 is the group $-CH_2OH$. This group may be modified by conventional techniques, thus, for example a compound of formula (I) wherein R^3 repres nts th group -CHO or $-CO_2H$ may be prepared by a stepwise oxidation using, for example, manganese dioxide, chromium trioxide in pyridine, or tetra-n-propylammonium perruthenate

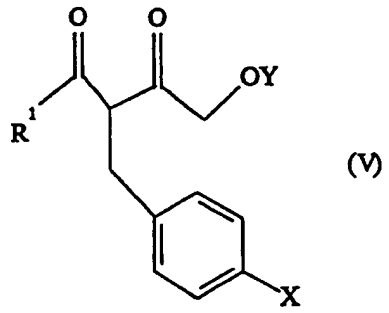
(TPAP) with 4-methylmorpholine-N-oxide to produce the aldehyde. Subsequent oxidation to the carboxylic acid may be effected using, for example, sodium chlorite with sodium dihydrogen orthophosphate, or potassium permanganate in the presence of acid, or chromic acid .

The compounds of formula (IV) are novel and represent a further aspect of the present invention.

It will be appreciated that inherent within the disclosure of the present invention will be the use of a compound of formula (IV) for the preparation of a compound of formula (Ia). Such use constitutes a further alternative aspect of the present invention.

As described above, the process of the present invention is a regioselective synthesis wherein the preferred isomer is ideally obtained in a ratio of at least 25:1, and preferably at least 40:1, in favour of the regioisomer shown in formula (Ia). Identification of the regioisomer obtained according to the process of the present invention may be achieved by techniques well known in the art, for example, by nuclear magnetic resonance (n.m.r.) spectroscopy.

The compounds of formula (IV) may be prepared, for example, by the deprotection and subsequent cyclisation of a compound of formula (V)



(V)

wherein R^1 and X are as defined in general formula (I) and Y is a hydroxyl protecting group, for example, an alkyl ether such as a t-butyl ether, an optionally substitut d benzyl ther such as p-methoxybenzyl ether, a silyl ether such as a t-butyldimethylsilyl or t-butyldiphenylsilyl ether, or such as a tetrahydropyranyl ether.

Other suitable hydroxyl protecting groups, their method of formation and suitable means of deprotection are described in Chapter 2 of "Protective Groups in Organic Synthesis" (2nd Edition) by T W Greene and P G M Wuts, John Wiley & Sons, Inc. New York (1991).

Thus, for example, the above protecting groups may be removed under conditions of acid hydrolysis using a mineral acid such as hydrochloric acid, basic hydrolysis using a base such as sodium hydroxide, or using fluoride ions (in the case of the silyl ethers), or using an acidic ion exchange resin (in the case of tetrahydropyranyl ethers).

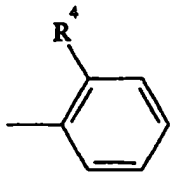
Particularly preferred protecting groups are silyl ethers, especially t-butyldimethylsilyl (TBDMS) ethers, especially where the compound of formula (V) contains other protecting groups, for example, where R^4 in the group X is a protected derivative of $-CO_2H$, a protected derivative of $-NH_2$ or a protected derivative of a C-linked tetrazolyl group. Removal of a silyl ether protecting group in such compounds, without affecting the protecting group in R^4, may be effected using the basic fluoride ion from, for example, tetrabutylammoniumfluoride (TBAF) in THF, or aqueous hydrogen fluoride in acetonitrile. Both of these deprotection reactions conveniently take place at room temperature.

Another particularly preferred protecting group is the tetrahydropyranyl (THP) ether group. Removal of a THP ether group may be effected by a number of techniques well known in the art. Particularly preferred are methods which utilise an acidic ion exchange resin such as Dowex™ 50W-X4 in methanol at room temperature.

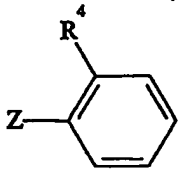
Intramolecular cyclisation of the hydroxymethyl diketone formed by the deprotection is preferably effected without purification of the hydroxymethyl diketone intermediate. Cyclisation is promoted by mild acid catalysis using, for example, dilute acid, e.g. hydrochloric acid, or silica gel or an acidic ion exchange resin.

It will be appreciated that where the hydroxymethyl protecting group is acid labile, deprotection and cyclisation may be effected in one step. Acidic deprotection and cyclisation may also result in the removal of any protecting group in th group R^4. It will be appreciated that, following formation of the furanone, any reactive group at R^4 may require further protection prior to any subsequent chemistry.

It will be appreciated that a compound of formula (IV) may be interconverted into another compound of formula (IV). For example, a compound of formula (IV) wherein X represents a halogen, especially chlorine, bromine or iodine, may be converted into a compound of formula (IV) wherein X represents a group of the formula



by reaction with a compound of formula (VI)



(VI)

wherein Z represents a halogen atom, especially iodine or the group $-B(OH)_2$ or an ester thereof, or an alkyltin derivative, e.g. tributyltin.

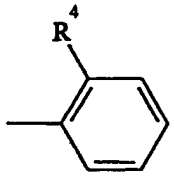
Where Z represents a halogen atom, especially iodine, the reaction may be effected in the presence of copper (the Ullman reaction). Alternatively, where Z represents a halogen atom, the compound of formula (VI) may form an organometallic intermediate with, for example, magnesium, lithium, zinc, aluminium, boron or tin. A coupling reaction with a compound of formula (IV) in which X represents a halogen atom may then be effected in the presence of a palladium catalyst, for example, tetrakis(triphenylphosphine)palladium(0). Particularly preferred is the reaction where Z represents the group $-B(OH)_2$.

It will be appreciated that, in the same manner, a compound of formula (IV) in which X is a halogen atom may be converted to the organometallic intermediate and then coupled to a compound of formula (VI) in which Z is a halogen atom.

These reactions may be effected in a suitable solvent such as an ther (e.g. 1,2-dimethoxyethan or tetrahydrofuran) or an aromatic hydrocarbon (e.g. benzene). The reactions are preferably carri d out in the presence of a base such as an alkali or alkaline arth metal carbonate (.g.

sodium bicarbonate) at a temperature between room temperature and the reflux temperature of the solvent.

Such biaryl couplings may also be effected prior to formation of the furanones of formula (IV), i.e. to prepare a compound of formula (V) in which X is the group



Alternatively, the biaryl coupling may be effected at any stage subsequent to the conversion of a furanone of formula (IV) into a pyrazole of formula (Ia).

The compounds of formula (V) may be prepared by methods analogous to those described in European Patent Specification No. 0446062A.

The following non-limiting examples serve to illustrate the present invention. Temperatures are in °C. "Dried" refers to drying using magnesium sulphate or sodium sulphate. Unless otherwise stated, thin layer chromatography (T.l.c.) was carried out on silica. Flash column chromatography (FCC) was carried out on silica gel (Merck 9385) unless otherwise stated. Nuclear magnetic resonance (n.m.r.) spectra were determined at 250MHz. The following solvent systems were used: System A - ether:hexane; System B - dichloromethane:ether; System C - ethyl acetate:hexane. The following abbreviations may be used: THF - tetrahydrofuran; DME - 1,2-dimethoxyethane; DMAP - 4-dimethylaminopyridine.

Intermediate 1

Methyl 1-[(1,1-dimethylethyl)dimethylsilyl]oxyacetate

t-Butyldimethylsilylchloride (222.4g) was added to an ice-cooled solution of methyl glycolate (127g) in dimethylformamide (950ml). Imidazole (100.4g) and then DMAP (4.1g) were added and the mixture heated at 40°C for 18h. The mixture was poured into water (300ml) and extracted with petroleum ether (3x1000ml). The combined extracts were washed with water (1000ml), aqueous copper sulphate (160g/1000ml), dried and

concentrated in vacuo to afford the title compound (271.4g) as a colourless liquid.

T.l.c. System A (1:1) Rf = 0.65

Example 1

3-Butyl-4-[[2'-[(2-triphenylmethyl)-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1-(1-methylethyl)-1H-pyrazole-5-methanol

(a) 1-[(1,1-Dimethylethyl)dimethylsilyl]oxy-2,4-octandione

2-Hexanone (35ml) in dry THF (20ml) was added dropwise to a stirred solution of lithium diisopropylamide (1.5M solution, 200ml) in dry THF (80ml) at -65 to -70°C under nitrogen. The mixture was stirred for 10min before dropwise addition of methyl 1-[(1,1-dimethylethyl)dimethylsilyl] oxyacetate (28.5g) in dry THF (50ml) at -70°C. The mixture was then stirred at 45°C, under nitrogen, for 24h. After the addition of saturated aqueous ammonium chloride (600ml) the mixture was extracted with ether (3x400ml). The combined organic extracts were washed with brine (2x400ml), dried and concentrated in vacuo to afford the title compound (31.9g) as a brown mobile oil.

T.l.c. petroleum ether:ether (50:1) Rf=0.24

(b) 1-[(1,1-Dimethylethyl)dimethylsilyl]oxy-3-[[2'-[(2-triphenylmethyl)-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-2,4-octandione

The product of step (a) (4.50g) in freshly distilled THF (25ml) was added dropwise to a rapidly stirred suspension of 60% sodium hydride (0.70g) in freshly distilled THF (250ml) causing rapid evolution of gas. After stirring for 30min a solution of 5-[4'-(bromomethyl)[1,1'-biphenyl]-2-yl]-2-(triphenylmethyl)-2H-tetrazole (described, for example, as Intermediate 3 in European Patent Specification No. 0446062A, published 11th September 1991) (6.7g) in anhydrous THF (25ml) was added dropwise and the resulting mixture heated at reflux under nitrogen overnight. Iced water (400ml) was added and the mixture adjusted to pH4 with 2N hydrochloric acid. The mixture was extracted with ether (3x250ml) and the combin d extracts washed with saturated brine (250ml), dried and

concentrated in vacuo to give a brown oil. FCC eluting with System A (1:10) gave the title compound as a yellow glass (4.69g)
T.l.c. System A (1:1) Rf = 0.32.

(c) 5-Butyl-4-[[2'-[(2-triphenylmethyl)-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-3(2H)-furanone
A solution of tetrabutylammoniumfluoride (1M in THF;155ml) was added to a stirred solution of the product of step (b) (38g) in THF (700ml) under nitrogen. The mixture was stirred at room temperature for 3h then ether (500ml) was added. The mixture was washed with 8% aqueous sodium bicarbonate (2x500ml) and brine (2x500ml) and then dried and concentrated in vacuo. The residue was dissolved in ether (1000ml) and dichloromethane (100ml). Silica (Merck 9385, 100g) was added and the mixture stirred for 48h. After filtering off the silica and removing the solvent in vacuo the material was purified by FCC eluting with System A (1:4) followed by dichloromethane:hexane:ether (20:30:5) to afford the title compound (9.8g) as a pale yellow foam.
T.l.c. hexane:dichloromethane:ether (30:20:5) Rf=0.28
n.m.r. ($CDCl_3$) δ 0.88 (3H,t), 1.3 (2H,m), 1.54 (2H,m), 2.42 (2H,t), 3.4 (2H,s), 4.47 (2H,s), 6.8-7.52 (22H,m), 7.88 (1H,dd).

(d) 3-Butyl-4-[[2'-[(2-triphenylmethyl)-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1-(1-methylethyl)-1H-pyrazole-5-methanol
A solution of the product of step (c) (850mg) in THF (5ml) and i-propylhydrazine (5ml) was allowed to stand under nitrogen at room temperature for 72h. Ether (100ml) was added and the mixture washed with water:saturated brine (10:1) (3x50ml) and saturated brine (50ml), dried and concentrated in vacuo to afford a yellow foam. Purification by FCC eluting with System B (9:1), gave the title compound as colourless foam (220mg).
T.l.c. System A (1:1) Rf=0.17
Mass Spec. (calc.) MH^+=673
(obs.) MH^+=673

Example 2

1,3-Dibutyl-4-[[2'-[(2-triphenylmethyl)-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-pyrazole-5-methanol

A solution of the product of step (c) of Example 1 (1.20g) in n-butylhydrazine (5ml) and freshly distilled THF (2.5ml) was allowed to stand overnight at room temperature under nitrogen. Ether (150ml) was added and the solution washed with water (3x75ml) and saturated brine (50ml), dried and concentrated in vacuo to afford a yellow oil. Trituration with System A (1:1) gave the title compound as a light yellow powder (1.15g).

T.l.c. ether Rf=0.71

n.m.r. ($CDCl_3$) δ 0.88 (3H,t) 0.93 (3H,t), 1.2-1.45 (5H,m), 1.54 (2H,m), 1.82 (2H,m), 2.51 (2H,t), 3.70 (2H,s), 4.08 (2H,t), 4.36 (2H,d), 6.88-7.53 (22H,m), 7.88 (1H,dd).

Example 3

3-Butyl-1-methyl-4-[[2'-[(2-triphenylmethyl)-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-pyrazole-5-methanol

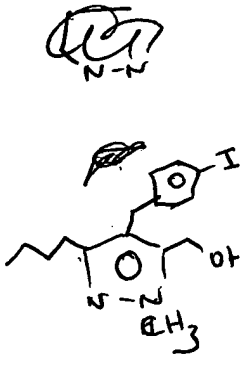
A solution of the product of step (c) of Example 1 (320mg) in freshly distilled THF (5ml) and methylhydrazine (5ml) was treated according to the method of step (d) of Example 1. Purification by FCC eluting with hexane:ethyl acetate:ethanol (100:20:1) gave the title compound as a colourless foam (180mg).

T.l.c. ethyl acetate Rf=0.65

n.m.r ($CDCl_3$) δ 0.88 (3H,t), 1.23-1.41 (2H,m), 1.56 (2H,m), 2.50 (2H,t), 3.70 (2H,s), 3.82 (3H,s), 4.33 (2H,s), 6.88-7.53 (22H,m), 7.87 (1H,dd).

Example 4

3-Butyl-4-[(4-iodophenyl)methyl]-1-methyl-1H-pyrazole-5-methanol



(a) 1-[(1,1-Dimethylethyl)dimethylsilyl]oxy-3-[(4-iodophenyl)methyl]-2,4-octandione

A solution of the product of step (a) of Example 1 (8.6g) in dry THF (50ml) was added slowly to a suspension of sodium hydride (60% dispersion in oil, 1.4g) in THF (50ml) with constant stirring under nitrogen. Aft r 15 minutes p-iodobenzylbromide (9.4g) in THF (150ml) was slowly added. The mixture was treated according to the method of step (b) of Example 1 to afford the title compound (16.3g) as a brown oil.

T.l.c. System A (1:4) Rf=0.52

(b) 5-Butyl-4-[(4-iodophenyl)methyl]-3(2H)-furanone

A solution of the product of step (a) (16.3g), concentrated hydrochloric acid (2ml) and dry THF (250ml) was stirred at room temperature under nitrogen for 16h. Ether (300ml) was added and the solution was washed with water (2x200ml), brine (2x200ml) and then dried. After concentrating in vacuo the material was purified by FCC eluting with System A (1:4) to afford the title compound (5.1g) as a yellow foam.

T.l.c. System A (1:4) Rf=0.15

n.m.r. ($CDCl_3$) δ 0.89 (3H,t), 1.32 (2H,m), 1.55 (2H,m), 2.48 (2H,t), 3.42 (2H,s), 4.48 (2H,s), 6.97 (2H, 1/2 AA'BB'), 7.58 (2H, 1/2 AA' BB').

(c) 3-Butyl-4-[(4-iodophenyl)methyl]-1-methyl-1H-pyrazole-5-methanol

A solution of the product of step (b) (560mg) in freshly distilled THF (10ml) and methylhydrazine (5ml) was heated at reflux for 6h. Ether (100ml) was added and the mixture extracted with water (3x100ml). The ethereal phase was washed with saturated brine (100ml), dried and concentrated in vacuo to give an orange oil. Purification by FCC eluting with ether gave the title compound as a light yellow solid (200mg)

T.l.c. ether Rf = 0.38

n.m.r. ($CDCl_3$) δ 0.85 (3H,t), 1.29 (2H,m), 1.46 (2H,m), 2.42 (2H,t), 2.84 (1H,br.s), 3.70 (2H,s), 3.79 (3H,s), 4.49 (2H,s), 6.84 (2H, 1/2 AA' BB'), 7.55 (2H, 1/2 AA'BB').

Example 5

1-(1-Methylethyl)-3-propyl-4-[2'-[(2-triphenylmethyl)-2H-tetrazol-5-yl] [1,1'-biphenyl-4-yl]methyl]-1H-pyrazole-5-methanol

(a) 1-[(1,1-Dimethylethyl)dimethylsilyl]oxy-2,4-heptandione

Prepared according to the method of step (a) of Example 1 using 2-pentanon (30ml) in the place of 2-h xanon .

T.l.c. 5% ether in petroleum ther Rf=0.58

(b) 1-[(1,1-Dimethylethyl)dimethylsilyl]oxy-3-[[2'-[(2-triphenylmethyl) -2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-2,4-heptandione

Prepared from the product of step (a) according to the method of step (b) of Example 1.
T.l.c. System A (1:4) Rf=0.13

(c) 5-Propyl-4-[[2'-[(2-triphenylmethyl)-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-3(2H)-furanone
Prepared from the product of step (b) according to the method of step (c) of Example 1.
T.l.c. Petroleum ether:dichloromethane:ether (30:20:5) Rf =0.23
n.m.r. ($CDCl_3$) δ 0.89 (3H,t), 1.58 (2H,m), 2.39 (2H,t), 3.4(2H,s), 4.47 (2H,s), 6.85-7.53 (22H,m), 7.88 (1H,dd).

(d) 1-(1-Methylethyl)-3-propyl-4-[[2'-[(2-triphenylmethyl)-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-pyrazole-5-methanol
Prepared from the product of step (c) according to the method of step (d) of Example 1.
T.l.c. ether Rf = 0.74
n.m.r. ($CDCl_3$) δ 0.9 (3H,t), 1.16 (1H,t), 1.47 (6H,d), 1.58 (2H,m), 2.51 (2H,t), 3.7(2H,s), 4.35 (2H,d), 4.55 (1H,m), 6.85-7.53 (22H,m), 7.88 (1H,dd).

Example 6
4'-[[3-Butyl-5-hydroxymethyl-1-(1-methylethyl)-1H-pyrazol-4-yl]methyl][1,1'-biphenyl]-2-carbonitrile
(a) 1-[(Tetrahydro-2H-pyran-2-yl)oxy]-2,4-octandione
Prepared according to the method of step (a) of Example 1 using 2-hexanone (148ml), lithium diisopropylamide (1.5M in THF; 800ml) and methyl 1-[(tetrahydro-2H-pyran-2-yl)oxy]acetate (104.5g) to give the title compound as a yellow oil (88g).
T.l.c. System A (1:9) Rf = 0.15

(b) 4'-[3-Oxo-2-[[(tetrahydro-2H-pyran-2-yl)oxy]acetyl]heptanyl][1,1'-biphenyl]-2-carbonitrile
Prepared from the product of step (a) (24.2g) according to the method of step (b) of Example 1 using sodium hydride (60%, 4.76g), 4'-

(bromomethyl)[1,1'-biphenyl]-2-carbonitrile (22g) and potassium iodide (16.5g) to give the title compound as a yellow oil (25g).
T.l.c. System A (1:1) Rf = 0.38

(c) 4'-[(2-Butyl-4,5-dihydro-4-oxo-furanyl)methyl][1,1'-biphenyl]-2-carbonitrile
Prepared from the product of step (b) (20.1g) according to the method of step (b) of Example 7 using Dowex™ 50 WX4 cationic exchange resin (8g) to give the title compound as a yellow oil (10.5g).
T.l.c. System C (1:4) Rf = 0.33
n.m.r. ($CDCl_3$) δ 0.9 (3H,t), 1.35 (2H,m), 1.58 (2H, pent), 2.54 (2H,t), 3.56 (2H,s), 4.52 (2H,s), 7.31-7.33 (2H,d), 7.38-7.5 (4H,m), 7.58-7.67 (1H,m), 7.72-7.76 (1H,dd).

(d) 4'-[[3-Butyl-5-hydroxymethyl-1-(1-methylethyl)-1H-pyrazol-4-yl] methyl][1,1'-biphenyl]-2-carbonitrile
Prepared from the product of step (c) (13.8g) according to the method of step (d) of Example 1 using isopropylhydrazine (55ml) to give the title compound as a pale yellow oil (14.8g).
T.l.c. System A (2:1) Rf = 0.31
n.m.r. ($CDCl_3$) δ 0.87 (3H,t), 1.34 (2H,m), 1.45-1.58 (8H,m), 2.55 (2H,t), 3.87 (2H,s), 4.53 (2H,s), 4.62 (1H,hept), 7.22-7.26 (2H,d), 7.39-7.51 (4H,m), 7.59-7.67 (1H,m), 7.73-7.77 (1H,dd).

Example 7
3-Butyl-4-[[2'-[(2-triphenylmethyl)-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl-1-(1-methylethyl)-1H-pyrazole-5-methanol
(Alternative preparation)
(a) 1-[(Tetrahydro-2H-pyran-2-yl)oxy]-3-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-2,4-octandione
Prepared from the product of step (a) of Example 6 (3g) according to the method of step (b) of Example 1 to give the title compound as a white solid (4.86g).
T.l.c. System A (1:1) Rf = 0.25

(b) 5-Butyl-4-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-3(2H)-furanone

A solution of the product of step (a) (3.8g) in methanol (15ml)/dichloromethane (10ml) was added to Dowex™ 50 WX4 (2g) [which had previously been washed with methanol (3x10ml)] in methanol (10ml) and the mixture stirred vigourously for 16h. The mixture was filtered and the solvent evaporated in vacuo to give the title compound as a pale yellow gum (3.5g).

T.l.c. System A (1:1) Rf = 0.15

(c) 5-Butyl-4-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-3(2H)-furanone

Triphenylmethyl chloride (164mg) was added in one portion to a solution of the product of step (b) (220mg), triethylamine (0.16ml) and DMAP (5mg) in dry dichloromethane (10ml) at room temperature under nitrogen, and the mixture stirred for 16h. The solution was then washed with water (2x10ml) and dried. The solvent was evaporated to give the title compound as a colourless foam (416mg).

T.l.c. ethyl acetate:petroleum ether (1:1) Rf = 0.8

NB: This compound is the same as the product of step (c) of Example 1.

(d) 3-Butyl-4-[[2'-[(2-triphenylmethyl)-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1-(1-methylethyl)-1H-pyrazole-5-methanol

A solution of the product of step (c) (1.00g) in iso-propylhydrazine (5ml) was heated at 75°C for 75h. Water (100ml) and saturated brine (10ml) were added and the mixture extracted with ether (3x50ml). The combined extracts were washed with water (2x50ml) and saturated brine (50ml), dried and concentrated in vacuo to afford a yellow solid. Trituration with System A (1:10) gave the title compound as a white powder (0.75g).

NB: This compound is the same as the product of step (d) of Example 1.

Exampl 8

3-Butyl-1-cyclopropylmethyl-4-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-pyrazole-5-methanol

Prepared from the product of step (c) of Example 1 (4.5g) according to the method of step (d) of Example 1 using cyclopropylmethylhydrazine (1.95g) to give the title compound as a white foam (3.25g).
T.l.c. System A (1:1) Rf =0.19
n.m.r. ($CDCl_3$) δ 0.3-0.6 (4H,m), 0.8-0.9 (4H,m), 1.2-1.6 (5H,m), 2.51 (2H,m), 3.62 (2H,s), 3.98 (2H,d), 4.38 (2H,d), 6.8-7.9 (23H, m).

Example 9
3-Butyl-1-propyl-4-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-pyrazole-5-methanol
Prepared from the product of step (c) of Example 1 (1.6g) according to the method of step (d) of Example 1 using n-propylhydrazine (640mg) to give the title compound as a yellow gum (1.82g).
T.l.c. System B (25:2) Rf = 0.27
n.m.r. ($CDCl_3$) δ 0.87 and 0.91 (6H,t+t), 1.2-1.9 (7H,m), 2.50 (2H,m), 3.71 (2H,s), 4.36 (2H,brs), 6.9-7.9 (23H, m).

Example 10
1,3-Dibutyl-4-(phenylmethyl)-1H-pyrazole-5-methanol
(a) 3-(Phenylmethyl)-1-[(tetrahydro-2H-pyran-2-yl)oxy]-2,4-octandione
Prepared from the product of step (a) of Example 6 (10g) according to the method of step (b) of Example 1 using benzylbromide (4.9ml) to give the title compound as yellow oil (14g).
T.l.c. System A (1:8) Rf =0.17

(b) 5-Butyl-4-(phenylmethyl)-3(2H)-furanone
A suspension of Dowex™ 50 WX4 cationic exchange resin (7.3g) in a solution of the product of step (a) (14g) in methanol (200ml) was rapidly stirred at room temperature for 2h. The mixture was filtered and the filtrate concentrated in vacuo. The residue was purified by FCC eluting with System A (3:7) to give the title compound as a yellow oil (5.3g).
T.l.c. System B (3:7) Rf = 0.31
n.m.r. ($CDCl_3$) δ 0.87 (3H,t), 1.31 (2H,m), 1.53 (2H,m), 2.48 (2H,m), 3.48 (2H,s), 4.47 (2H,s), 7.1-7.3 (5H,s),

(c) 1,3-Dibutyl-4-(phenylmethyl)-1H-pyrazole-5-methanol

Prepared from the product of step (b) (1g) according to the method of step (c) of Example 4 using n-butylhydrazine (3.3g) to give the title compound as a yellow oil (1.07g).

T.l.c. System B (11:1) Rf = 0.50

n.m.r. ($CDCl_3$) δ 0.87 and 0.93 (6H, t+t), 1.2-1.8 (7H,m), 2.53 (2H,m), 3.80 (2H,s), 4.09 (2H,m), 4.47 (2H,d), 7.1-7.3 (5H,m).

Example 11

3-Butyl-1-(1-methylethyl)-4-(phenylmethyl)-1H-pyrazole-5-methanol

Prepared from the product of step (b) of Example 10 (1g) according to the method of step (c) of Example 4 using isopropylhydrazine (5ml) to give the title compound as a white solid (0.9g).

T.l.c. System A (2:1) Rf = 0.50

n.m.r. ($CDCl_3$) δ 0.87 (3H,m), 1.150 (1H,t), 1.32 (2H,m), 1.49 (6H,d), 1.50 (2H,m), 2.56 (2H,m), 3.81 (2H,s), 4.48 (2H,d), 4.58 (1H,m), 7.1-7.3 (5H,m).

Example 12

4-[(2-Butyl-4,5-dihydro-4-oxo-3-furanyl)methyl][1,1'-biphenyl]-2-carbonitrile

[Alternative Procedures to the product of step (c) of Example 6]

(a) 5-Butyl-4-[(4-iodophenyl)methyl]-3(2H)-furanone

Trifluoroacetic acid (0.2ml) was added to a solution of the product of step (a) of Example 4 (1g) in dry THF (15ml) at room temperature under nitrogen. The mixture was stirred for 4h, then heated at 60°C for 2h. The mixture was cooled to room temperature and concentrated hydrochloric acid (0.2ml) was added. The mixture was stirred for 2h, concentrated (to 5ml) and diluted with ether (25ml). The solution was washed with water (2x20ml), then brine (20ml) and dried. The solvent was evaporated to give the title compound as a pale orange gum (772mg).

T.l.c. System A (1:4) Rf = 0.15.

(b) 4-[(2-Butyl-4,5-dihydro-4-oxo-3-furanyl)methyl][1,1'-biphenyl]-2-carbonitrile

[Alternative Prep.1]

A mixture of the product of step (a) (250mg), 2-cyanobenzeneboronic acid (113mg), tetrakis(triphenylphosphine)palladium(0) (14mg) and aqueous sodium carbonate (1N; 10ml) in 'peroxide free' DME (20ml) was heated under reflux for 4h. The cooled mixture was partitioned between water (100ml) and ethyl acetate (3x100ml). The combined organic extracts were washed with sodium carbonate (2N;100ml), then brine (100ml) and dried. The solvent was evaporated and the residue purified by FCC eluting with ether to give the title compound as a pale yellow oil (30mg).
T.l.c. ether Rf = 0.71.

Alternative Prep 2.

A mixture of the product of step (a) (250mg), 2-cyanobenzeneboronic acid (113mg), silver (I) oxide (325mg) and tetrakis (triphenylphosphine)palladium(0) (14mg) in dry THF (20ml) was stirred at room temperature for 18h. Further portions of the boronic acid (113mg), tetrakis(triphenylphosphine)palladium(0) (14mg) and silver (I) oxide (325mg) were added and the mixture was stirred for 16h at 60°. The cooled mixture was filtered through hyflo and the solvent evaporated. The residue was purified by FCC eluting with ether to give the title compound as a pale yellow oil (113mg).
T.l.c. ether Rf = 0.71

Alternative Prep. 3

A mixture of the product of step (a) (150mg), 2-cyanobenzeneboronic acid (88mg), potassium phosphate (tribasic, 254mg) and tetrakis (triphenylphosphine)palladium(0) (5mg) in dry dioxan (2ml) was heated at 80° for 16h. The cooled mixture was partitioned between sodium carbonate (2N, 10ml) and dichloromethane (3x20ml). The combined organic extracts were dried and evaporated to give a brown oil (163mg). The crude material was purified by FCC eluting with petroleum ether:ether (7:3) to give the titl compound as a pal yellow oil (47mg).
T.l.c. Syst m A (6:4) Rf = 0.3

Alternative Pr p. 4

n-Butyl lithium (1.57M; 0.95ml) was added dropwise to a solution of 2-bromobenzonitrile (271mg) in dry THF (5ml) at -75 to -70° under nitrogen. The mixture was stirred at -75° for 20min, then a solution of zinc chloride (1M; 1.5ml) in ether was added dropwise at -75°. The mixture was stirred for 10min, then tetrakis(triphenylphosphine)palladium (0) (18mg) and the product of step (a) in THF (2ml) were added sequentially. The mixture was allowed to warm to room temperature and was then heated under reflux for 18h. The cooled mixture was partitioned between ether (3x15ml) and hydrochloric acid (0.1M; 15ml). The combined organic extracts were washed with brine (20ml) and dried. The solvent was evaporated and the residue was purified by FCC eluting with petroleum ether:ether (4:1) to give the title compound as a pale yellow oil (114mg).
T.l.c. System A (6:4) Rf = 0.3

The following preparations illustrate further modifications of the pyrazole compounds formed according to the process of the present invention in Examples 1 to 12 above:

Preparation A

(i) 3-Butyl-4-[[2'-[(2-triphenylmethyl)-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1-(1-methylethyl)-1H-pyrazole-5-carboxaldehyde

A mixture of the product of Example 1 (4.3g), manganese dioxide (5g) and freshly distilled THF (20ml) was heated at 50°C for 24h. Further manganese dioxide (5g) was added and the mixture heated at 50°C for a further 24h. The mixture was filtered through hyflo and the filtrate concentrated in vacuo to give an off-white foam. Purification by FCC eluting with System A (1:2) gave the title compound as a white foam (2.8g).
T.l.c. System A (1:1) Rf=0.75

(ii) 3-Butyl-4-[[2'-[(2-triphenylmethyl)-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1-(1-methylethyl)-1H-pyrazole-5-carboxylic acid

A solution of sodium chlorite (80%, 4.47g) and sodium dihydrogen orthophosphate (4.47g) in water (50ml) was added to a stirred solution of

the product of preparation A(i) (2.65g) in freshly distilled THF (50ml), t-butanol (50ml) and 2-methylbut-2-ene (24ml) and the mixture vigorously stirred overnight at room temperature. The mixture was concentrated in vacuo to 75ml, water (150ml) added and the mixture extracted with ethyl acetate (3x100ml). The combined extracts were washed with saturated brine (200ml), dried and concentrated in vacuo to afford the title compound as a white foam (3.0g).
n.m.r. ($CDCl_3$) δ 0.84 (3H,t), 1.28 (2H,m), 1.41-1.6 (8H, d+m), 2.47 (2H,t), 4.0 (2H,s), 5.39 (1H,m), 6.85-7.5 (22H,m), 7.87 (1H,dd).

(iii) 3-Butyl-4-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1-(1-methylethyl)-1H-pyrazole-5-carboxylic acid
A solution of the product of preparation A (ii) (3.00g) and conc. hydrochloric acid (1ml) in ethanol (25ml) was stirred at room temperature for 5h. 8% w/v Aqueous sodium hydrogen carbonate (100ml) was added and the mixture concentrated to 100ml. The mixture was extracted with ether (4x50ml) and the extracts discarded. The aqueous phase was acidified to pH2 with 2N hydrochloric acid and extracted with ethyl acetate (3x100ml). The combined extracts were washed with saturated brine (100ml), dried and concentrated in vacuo to give the title compound as a white powder (1.50g).

Assay Found:	C,67.8; H,6.4; N,18.5;
$C_{25}H_{28}N_6O_2$ requires:	C,67.55; H,6.35; N,18.9%

Preparation B

(i) 1,3-Dibutyl-4-[[2'-[(2-triphenylmethyl)-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-pyrazole-5-carboxaldehyde
Prepared from the product of Example 2 according to the method of preparation A(i).
T.l.c. ether:petroleum ether (1:1) Rf=0.66

(ii) 1,3-Dibutyl-4-[[2'-[(triphenylmethyl)-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-pyrazole-5-carboxylic acid
Prepared from the product of preparation B(i) according to the method of preparation A(ii).

n.m.r. ($CDCl_3$) δ 0.84 (3H,t), 0.92 (3H,t), 1.18-1.56(6H,m), 1.78 (2H,m), 2.46 (2H,t), 4.0 (2H,s), 4.48 (2H,t) 6.84-7.57 (22H,m), 7.87 (1H,dd).

(iii) 1,3-Dibutyl-4-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-pyrazole-5-carboxylic acid

Prepared from the product of preparation B(ii) according to the method of preparation A(iii).

m.p. 180-185°C.

Preparation C

3-Butyl-4-[[2'-[(2-triphenylmethyl)-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl] methyl]-1-methyl-1H-pyrazole-5-carboxaldehyde

A suspension of manganese dioxide (750mg) in a solution of the product of Example 3 (300mg) in freshly distilled THF (10ml) was rapidly stirred at room temperature under nitrogen overnight. Further manganese dioxide (500mg) was added and the suspension stirred for another 6h. The mixture was filtered through hyflo and the filtrate concentrated in vacuo to give the title compound as a colourless foam (200mg).

T.l.c. ether Rf=0.65

Preparation D

(i) 1-(1-Methylethyl)-3-propyl-4-[[2'-[(2-triphenylmethyl)-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-pyrazole-5-carboxaldehyde

Prepared from the product of Example 5 according to the method of preparation A(i).

T.l.c. System A (3:7) Rf=0.45

(ii) 1-(1-Methylethyl)-3-propyl-4-[[2'-[(2-triphenylmethyl)-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-pyrazole-5-carboxylic acid

Prepared from the product of preparation D(i) according to the method of preparation A(ii).

T.l.c. System A (1:1) Rf=0.5

(iii) 1-(1-Methylethyl)-3-propyl-4-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-pyrazole-5-carboxylic acid

Prepared from the product of preparation D(ii) according to the method of preparation A(iii).

Assay Found: C,67.3; H,6.2; N,19.5;

$C_{24}H_{26}N_6O$ requires: C,67.0; H,6.1; N,19.5%

Preparation E

(i) 4'-[[3-Butyl-5-formyl-1-(1-methylethyl)-1H-pyrazol-4-yl]methyl][1,1'-biphenyl]-2-carbonitrile

Prepared from the product of Example 6 (5.0g) according to the method of preparation A(i) using manganese dioxide (6.5g) in a mixture of dichloromethane and dioxan (2:1) (150ml) to give the title compound as an orange oil (3.81g).

T.l.c. System A (1:1) Rf = 0.61.

(ii) 3-Butyl-4-[(2'-cyano-[1,1'-biphenyl]-4-yl)methyl]-1-(1-methylethyl)-1H-pyrazole-5-carboxylic acid

Prepared from the product of preparation E(i) (3.81g) according to the method of preparation A(ii) using sodium chlorite (80%; 2.3g), sodium dihydrogen orthophosphate (4.87g), t-butanol (65ml) and 2-methylbut-2-ene (4.21g) to give the title compound as a yellow oil (3.62g).

T.l.c. System A (1:1) Rf = 0.42

Preparation F

(i) 3-Butyl-1-cyclopropylmethyl-4-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-pyrazole-5-carboxaldehyde

Prepared from the product of Example 8 (3.0g) according to the method of preparation A(i) using manganese dioxide (9g) to give the title compound as a white foam (2.5g).

T.l.c. System A (1:1) Rf = 0.64

(ii) 3-Butyl-1-cyclopropylmethyl-4-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-pyrazole-5-carboxylic acid

Prepared from the product of preparation F(i) (2.5g) according to the method of pr paration A(ii) using sodium chlorite (80%; 4.47g), t-butanol

(50ml), sodium dihydrogen orthophosphate (4.47g) and 2-methylbut-2-ene (24ml) to give the title compound as a white foam (2.4g).
T.l.c. System A (1:1) Rf 0.29

(iii) 3-Butyl-1-cyclopropylmethyl-4-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-pyrazole-5-carboxylic acid
Prepared from the product of preparation F(ii) (2.3g) according to the method of preparation A(iii) using concentrated hydrochloric acid (1ml) to give the title compound as a white solid.

Assay Found:	C,68.6; H,6.2; N,18.3;
$C_{26}H_{28}N_6O_2$ requires	C,68.4; H,6.2; N,18.4%

Preparation G

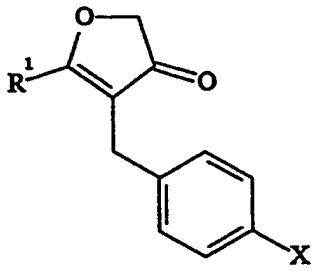
(i) 3-Butyl-1-propyl-4-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-pyrazole-5-carboxaldehyde
Prepared from the product of Example 9 (420mg) according to the method of preparation A(i) using manganese dioxide (1g) to give the title compound as a yellow oil (350mg).
T.l.c. System B (20:1) Rf = 0.88

(ii) 3-Butyl-1-propyl-4-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-pyrazole-5-carboxylic acid
Prepared from the product of preparation G(i) (350mg) according to the method of preparation A(ii) using sodium chlorite (80%; 465mg), t-butanol (5ml), sodium dihydrogen orthophosphate (465mg) and 2-methylbut-2-ene (3.2ml) to give the title compound as a white foam (380mg).
T.l.c. System B (20:1) Rf =0.34

(iii) 3-Butyl-1-propyl-4-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-pyrazole-5-carboxylic acid
Prepared from the product of preparation G(ii) (90mg) according to the method of preparation A(iii) using concentrated hydrochloric acid (0.1ml) to give the title compound as a white solid (46mg).
n.m.r. ($CDCl_3$) δ 0.86 and 0.90 (6H,t+t), 1.2-1.9 (6H,m), 2.49 (2H,m), 4.08 (2H,s), 4.47 (2H,m), 7.0-7.8 (8H, m).

Claims

1. A compound of formula (IV)

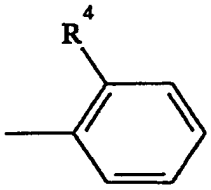


(IV)

wherein

R^1 represents a hydrogen atom or a group selected from C_{1-6}alkyl or C_{2-6}alkenyl;

X represents a halogen atom or a group of the formula



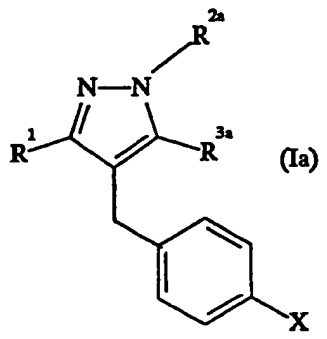
; and

R^4 represents a group selected from $-NH_2$, -CN, or a protected derivative of $-CO_2H$, a protected derivative of a C-linked tetrazolyl group.

2. A compound as claimed in Claim 1 wherein R^1 represents a C_{1-5}alkyl group.

3. A compound as claimed in Claim 2 wherein the C_{1-5}alkyl group is an ethyl, n-propyl or n-butyl group.

4. Use of a compound of formula (IV) as claimed in Claim 1 for the preparation of a compound of formula (Ia)


(Ia)

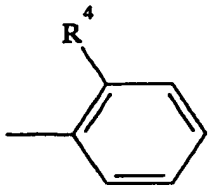
wherein

R^1 represents a hydrogen atom or a group selected from C_{1-6}alkyl or C_{2-6}alkenyl;

R^{2a} represents a hydrogen atom or a group selected from C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, C_{3-6}alkenyl, fluoroC_{1-6}alkyl, fluoroC_{3-6}alkenyl;

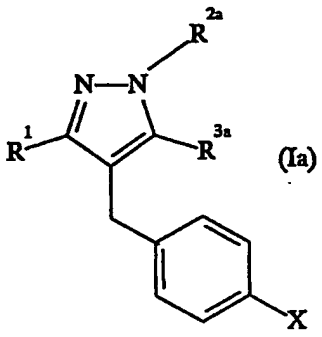
R^{3a} represents a hydroxymethyl group;

X represents a hydrogen atom or a halogen atom or a group of the formula


; and

R^4 represents a group selected from $-NH_2$, -CN, or a protected derivative of $-CO_2H$, a protected derivative of $-NH_2$ or an optionally protected C-linked tetrazolyl group.

5. A process for the preparation of a compound of formula (Ia)



(Ia)

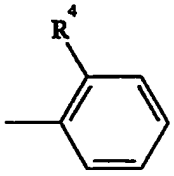
wherein

R^1 represents a hydrogen atom or a group selected from C_{1-6}alkyl or C_{2-6}alkenyl;

R^{2a} represents a hydrogen atom or a group selected from C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, C_{3-6}alkenyl, fluoroC_{1-6}alkyl, fluoroC_{3-6}alkenyl;

R^{3a} represents a hydroxymethyl group;

X represents a hydrogen atom or a halogen atom or a group of the formula

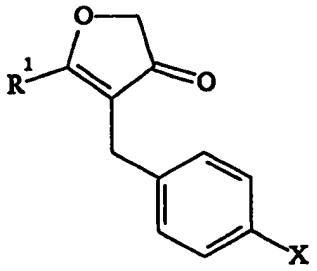


;

R^4 represents a group selected from $-NH_2$, -CN, or a protected derivative of $-CO_2H$, a protected derivative of $-NH_2$ or an optionally protected C-linked tetrazolyl group;

which comprises:

reacting a compound of formula (IV)



(IV)

wherein R^1 and X are as defined above, with a hydrazine of formula (III)

$$R^2NHNH_2 \qquad (III)$$

wherein R^2 is as defined above.

6. A process as claimed in Claim 5 which comprises the reaction of a compound of formula (IV) wherein R^1 represents a C_{1-5}alkyl group, with a compound of formula (III) wherein R^2 represents a C_{1-5}alkyl group.

7. A process as claimed in Claim 6 wherein the C_{1-5}alkyl group of R^1 in the compound of formula (IV) is an ethyl, n-propyl or n-butyl group.

8. A process as claimed in Claim 6 wherein the C_{1-5}alkyl group of R^2 in the compound of formula (III) is an ethyl, isopropyl or n-butyl group.

9 A process as claimed in Claim 5 wherein R^2 represents a C_{3-5}cycloalkylC_{1-2}alkyl group.

10. A process as claimed in Claim 9 wherein the C_{3-5}cycloalkylC_{1-2}alkyl group is a cyclopropylmethyl group.

Patents Act 1977
Examiner's report to the Comptroller under Section 17 (The Search Report)

Application number
GB 9307342.7

Relevant Technical fields

(i) UK Cl (Edition L) C2C CMD CTZ

(ii) Int Cl (Edition 5) C07D

Search Examiner
P N DAVEY

Databases (see over)

(i) UK Patent Office

(ii) ONLINE DATABASES: CAS ONLINE

Date of Search
2 JUNE 1993

Documents considered relevant following a search in respect of claims 1-10

Category (see over)	Identity of document and relevant passages	Relevant to claim(s)
A	EP 0446062 A1 (GLAXO) See eg. Claim 1	4-10

Category	Identity of document and relevant passages	Relevant to claim(s)

Categories of documents

X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

A: Document indicating technological background and/or state of the art.

P: Document published on or after the declared priority date but before the filing date of the present application.

E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family, corresponding document.

Databases: The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).